

THE AMYGDALA AND REWARD

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The amygdala — an almond-shaped group of nuclei at the heart of the telencephalon — has been associated with a range of cognitive functions, including emotion, learning, memory, attention and perception. Most current views of amygdala function emphasize its role in negative emotions, such as fear, and in linking negative emotions with other aspects of cognition, such as learning and memory. However, recent evidence supports a role for the amygdala in processing positive emotions as well as negative ones, including learning about the beneficial biological value of stimuli. Indeed, the amygdala's role in stimulus–reward learning might be just as important as its role in processing negative affect and fear conditioning.

It is widely accepted that the amygdala is important for the recognition of negative, unpleasant emotions, such as fear, and for associating environmental stimuli with emotionally charged, aversive sensory inputs. Recent reviews of the neuropsychology of the amygdala have focused largely on its role in fear and in fear conditioning^{1,2}, or in the response to arousing negative events³, mentioning its involvement in positive affect in passing, if at all (but see REFS 4,5). However, there is considerable experimental evidence that the amygdala has a role in the processing of positive emotions, particularly in specific kinds of stimulus–reward learning. This review explores selected aspects of this evidence.

Contributions from experimental neuropsychology and neurophysiology indicate that two main amygdala–output pathways (FIG. 1) contribute in different ways to the processing of information about reward. There is ample evidence that several other brain structures also represent reward and guide behaviour on the basis of reward expectation. To carry out its reward-related functions, the amygdala interacts with an array of cortical and subcortical structures, including the nucleus accumbens (part of the striatum), the midbrain dopaminergic system (the substantia nigra and the ventral tegmental area), the basal forebrain cholinergic system and the prefrontal cortex, particularly its medial and orbital parts. Accordingly, clarification of the specific roles of the amygdala in reward processing might provide a foundation for a better understanding of the many functions that are affected by reward, including learning and memory, addiction and the mechanisms that underlie goal-directed action.

Stimulus–reward learning revisited

Many early studies in rodents and non-human primates identified a role for the amygdala in stimulus–reward learning — the association of reward value with initially neutral stimuli — as measured by performance on visual-discrimination learning or reversal tasks, and win–stay, lose–shift tasks^{6,7}. In such tasks, animals need to learn which stimulus or place to choose in order to obtain a reward (usually food or water). In visual discrimination, the animal learns to choose one stimulus (designated S⁺) rather than a distracter stimulus (S⁻). In reversals, the S⁻ becomes the S⁺, and vice versa. In win–stay, lose–shift tasks, animals might return to a place that led to success and avoid a place that led to failure in producing rewards.

Aspiration lesions, in which most or all of the amygdala is removed mechanically, produce severe impairments in several measures of stimulus–reward learning^{8–13}. These early findings indicated that, in non-human primates, the amygdala has a fairly general role in associating stimuli with their reward value, and indicated that the amygdala is important in remembering the features of stimuli. Unfortunately, the techniques used in these experiments made it impossible to distinguish the effects of damage to the amygdala from those of damage to axons passing through or near to the amygdala. Selective lesions of the amygdala or of its component nuclear groups in non-human primates have become possible only relatively recently, with the development of magnetic resonance imaging (MRI)-guided stereotaxic approaches

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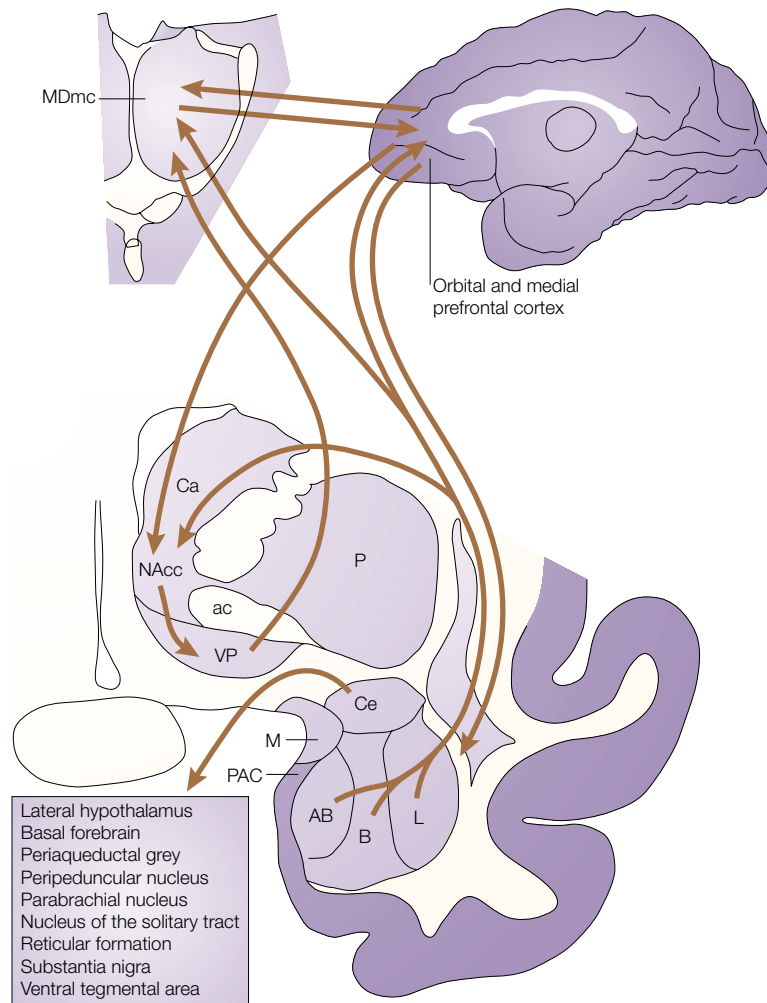


Figure 1 | Anatomical relationships of the basolateral complex and the central nucleus of the amygdala in macaque monkeys. The basolateral complex of the amygdala consists of the lateral nucleus (L), the basal nucleus (B) and the accessory basal nucleus (AB). Each of these nuclei contains neurons that project directly to the nucleus accumbens (NAcc), a part of the ventral striatum, and to the medial, magnocellular portion of the mediodorsal nucleus of the thalamus (MDmc). In addition, the basolateral complex is reciprocally connected to the orbital and medial prefrontal cortex. The central nucleus (Ce) projects to numerous forebrain structures and brainstem nuclei. ac, anterior commissure; Ca, caudate; M, medial nucleus of amygdala; P, putamen; PAC, periamygdaloid cortex; VP, ventral pallidum. Adapted, with permission, from REF. 88 © 1996 Elsevier Science.

EXCITOTOXIN

A chemical toxin — typically a structural analogue of the neurotransmitter glutamate — that, when injected into brain tissue, kills cell bodies in the region of injection, leaving fibres of passage through that region intact. The neurotoxic effect of these agents is mediated by their action at glutamate receptors and involves overstimulation of the neuron, which leads to cell death.

combined with the injection of **EXCITOTOXINS**, which kill cell bodies, but spare most of the fibres that pass through or near to the targeted nucleus. Results that have been obtained by the application of these new techniques have overturned many earlier ideas about amygdala function, especially those generated by work in non-human primates. As a consequence, parallels are emerging from work carried out in rodents and in non-human primates.

Experiments that have made use of excitotoxic lesions have, for example, failed to confirm previous results that pointed to a role for the amygdala in stimulus-recognition memory, as measured by the **DELAYED NONMATCHING-TO-SAMPLE** task, or in any of several alternative tests of stimulus memory^{14–17}. Accordingly, we now know that the amygdala is not necessary for storing

information about the physical features of objects, and that any impairment in learning about stimulus–reward associations that results from lesions to the amygdala is unlikely to reflect deficits in processing or representing attributes of the ‘stimulus’ part of the association. Furthermore, these new techniques have generally shown that the deficits that are observed in stimulus–reward learning are not as straightforward as was initially believed. For example, monkeys with selective damage to the amygdala are unimpaired in visual-discrimination learning^{18,19}, a simple task that is generally held to tap stimulus–reward learning. These findings do not rule out a role for the amygdala in the representation of reward, in learning about reward or in associative learning in general, but they do indicate that its involvement is much more selective than was previously believed.

The crux of the problem is that stimulus–reward learning is far from a unitary process, and neither reinforcement nor reward is an uncomplicated concept. Naturally occurring rewards include food, water and sex, and environmental stimuli that are linked to these types of reward can themselves become reinforcing. There are many aspects of reward, including: hedonic (liking) and incentive (wanting) value^{20,21}; variability in terms of probability, timing, quantity and quality; and consistency over time (for example, always rewarding, recently more rewarding, usually rewarding but not as much recently, and so on). Given the diversity of these aspects of reward, it is perhaps not surprising that learning about reward engages multiple neural systems.

Amygdala-independent reward processing

Several kinds of behaviour depend on reward processing but are, nevertheless, not dependent on the amygdala. In this section, we discuss five observations that highlight amygdala-independent forms of learning, including stimulus–reward learning: visual-discrimination learning, visuomotor conditional learning, food-cup approach, and food and object preferences. Given these examples, it is easy to see how the idea might develop that, because the amygdala is not important for positive affect and reward processing in these many instances, its fundamental role must be in the processing of negative affect.

Discrimination learning is a prototypical form of **INSTRUMENTAL LEARNING**. Monkeys are typically offered a choice between two objects. The same two objects are presented in pairwise fashion over a series of trials; one of the objects of the pair (S^+) is always baited (covers a small food reward, such as a half-peanut or a raisin), whereas the other is always unbaited (S^-). Over several training trials, monkeys learn consistently to select the baited object irrespective of its location. As noted above, complete removal of the amygdala does not disrupt this behaviour^{18,19}. There are other examples of intact instrumental learning in rats with amygdala damage^{22,23}. These findings do not imply that, in the absence of an amygdala, animals learn discrimination problems in an entirely normal manner, but they do indicate that there is a mechanism outside the amygdala that can mediate this type of learning.

In another form of instrumental learning, often termed conditional motor learning or conditional visual discrimination, monkeys must learn to associate a stimulus with a motor or spatial response. For example, a blue cube might instruct the monkey to move a joystick to the right, whereas a red cylinder instructs a movement to the left. The animals learn by trial and error, with only reward or non-reward on past trials to guide future responses. Again, complete bilateral removal of the amygdala has no effect on either learning or recall of these sensorimotor associations²⁴.

In simple appetitive PAVLOVIAN conditioning, a neutral stimulus, typically a light or tone, is paired with food delivery into a food cup. The initially neutral stimulus is called a conditioned stimulus (CS). Although no response is required, the animal begins to show food-related behaviours during the presentation of the light or tone; for example, by approaching the food cup. This behaviour indicates that an association has been learned between the stimulus and food delivery. This form of stimulus–reward learning, like the two examples mentioned above, is unaffected by damage to the amygdala^{25,26}.

Finally, animals in which the amygdala has been removed have well-documented food preferences^{14,27}. That is, like normal monkeys, they show stable preferences among a set of food items. Similarly, they can acquire object preferences for items that have been associated with particular foods¹⁸.

These findings, considered together, provide clear evidence that the amygdala is not important for all reward-based learning^{7,28}, and are consistent with the view that the amygdala is important for the processing of negative but not positive affective events.

Perhaps the most important of the foregoing examples, in terms of its influence in pointing away from a role in reward processing, is visual-discrimination learning. One straightforward solution to a visual-discrimination problem would rely on linking the stimulus to food reward; that is, stimulus–reward processing. Indeed, learning to approach and displace the S⁺ in a discrimination problem is often referred to as involving ‘stimulus–reward associations’. But this is just one way in which such problems can be solved. It seems that there are several mechanisms by which an animal can choose a stimulus on the basis of ‘reward’, and thereby solve visual-discrimination problems. Another solution involves stimulus–response associations. In conditional motor learning, which we discussed earlier, monkeys with amygdala lesions learn arbitrary associations between visual stimuli and responses as rapidly as controls. So, stimulus–response learning does not rely on the amygdala. Visual-discrimination problems can be solved using this same mechanism. According to this view, the ‘response’ is not necessarily a motor programme *per se*, but can be more abstract; for example, ‘given the choice between stimuli A and B, choose A’. Furthermore, we propose that the food-cup approach, which is the product of Pavlovian conditioning, might be mediated by this same mechanism. As in conditional motor learning and visual discrimination, the light

provides the context for an action (approach the food cup). This analysis indicates that an intact ability to solve visual-discrimination problems through instrumental conditioning and to acquire the food-cup approach through Pavlovian conditioning does not rule out a role for the amygdala in the processing of reward and positive affect.

Stimulus–response learning seems to account for three of the five behaviours that argue against a role for the amygdala in reward processing. What might underlie the intact food preferences and object preferences of animals that have no amygdala? One possibility is that stimulus representations that are stored in the cortex can be used to guide behaviour; recent evidence indicates that reward value is an intrinsic property of stimulus representations. Representation, in this sense, implies a high-dimensional set of properties, including those from several stimulus modalities, such as colour, shape, texture (visual and tactile), smell and so on. The concept of assigning a value to, and as part of, a representation is often called ‘affective valence’ and is related to the idea of salience maps. Given that foods are identified by their visual, gustatory and olfactory properties, values that are intrinsic to stimulus representations could underlie the acquisition of food preferences as well as object preferences. The cerebral cortex is the most likely extra-amygdalar site for the storage of these valuations. Neurophysiological evidence indicates that the value of objects and sensorimotor mappings is reflected in cortical activity. For example, Platt and Glimcher²⁹ showed that neurons in the posterior parietal cortex reflect both the probability and quantity of expected reward for a visuomotor response. There is similar evidence for the orbital frontal cortex^{30–34}. In the more purely sensory domain, Jagadeesh *et al.*³⁵ showed that responses of neurons of the inferotemporal cortex to objects were modulated by the affective valence of the objects, given the choice between an S⁺ and an S[−] stimulus. A rewarded stimulus or sensorimotor association could be encoded through the interaction of inferior temporal cortical areas with portions of the hypothalamus or basal forebrain^{36–38}, or with the mediodorsal thalamus and parts of the prefrontal cortex^{7,39}.

These two amygdala-independent mechanisms could support the five behaviours that we have discussed (visual-discrimination learning, conditional motor learning, food-cup approach, food preferences and object preferences). The circuits that mediate these behaviours might involve corticostriatal interactions^{40,41}, cortical sensorimotor interactions^{42,43}, or both. Although these data indicate that not all reward processing depends on the amygdala, they do not rule out a contribution of the amygdala to reward processing. This is the topic to which we now turn.

Amygdala-dependent reward processing

Basolateral complex. The basolateral complex of the amygdala seems to be especially important for linking objects with current stimulus value. In one of the amygdala-independent mechanisms described above, the animals learn to approach a stimulus that is consistently

DELAYED NONMATCHING-TO-SAMPLE

A test of stimulus-recognition memory in which the subject is presented with one or more sample objects and, after a short delay, is confronted with a choice test between the sample object and a novel object. The subject is rewarded for choosing the novel object.

INSTRUMENTAL LEARNING

Learning that takes place through reinforcement (or the absence of punishment) that is contingent on the performance (or withholding) of a particular behaviour. So, the subject's response is instrumental in producing an outcome, typically a food reward. Compare with Pavlovian learning.

PAVLOVIAN LEARNING

Learning that takes place because of temporal contiguity between a stimulus (the conditioned stimulus) and a reinforcer (the unconditioned stimulus), in the absence of a requirement for the subject to produce a particular behaviour to obtain reinforcement. Also commonly referred to as classical conditioning.

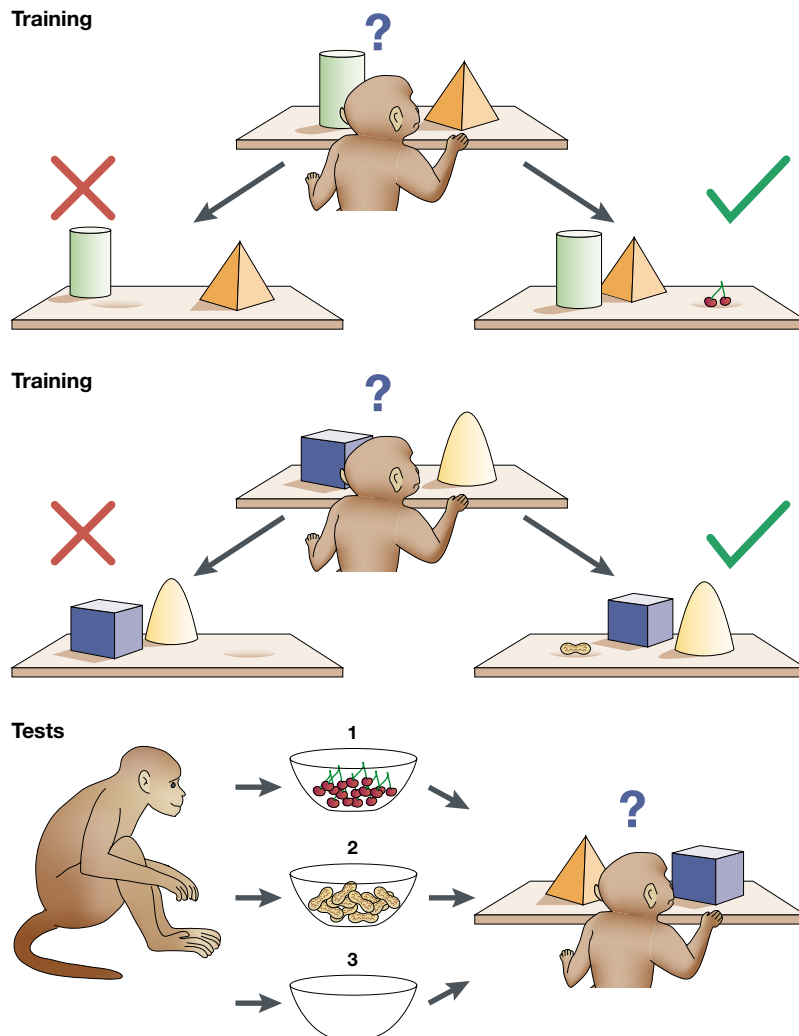


Figure 2 | Reinforcer-devaluation task. During the training phase, monkeys are familiarized with objects through daily test sessions that involve a large set of visual-discrimination problems. On each trial, two objects are presented; one object is always baited and the other is never baited. The monkeys learn to displace only those objects that overlie food rewards. Half of the positive objects always cover food 1 (for example, a peanut) and the other half always cover food 2 (for example, a cherry). Presumably, in the course of learning the visual discrimination, the monkeys also learn that some objects are ‘peanut objects’ and others are ‘fruit objects’. During the test phase, the fruit objects and peanut objects are presented in pairs, and the monkeys are required to choose between them. The object that is displaced dictates the type of food reward obtained on that trial. There are three kinds of test session: sessions that are preceded by feeding to satiety with fruit (1), sessions that are preceded by feeding to satiety with peanuts (2), and sessions with no prefeeding, which serve as a baseline (3). On those test sessions preceded by selective satiation, intact monkeys change their choices relative to baseline: they tend to avoid the objects that overlie the now devalued food in favour of the remaining objects. Monkeys with amygdala lesions, and monkeys with crossed disconnection of the amygdala and orbital prefrontal cortex, show little change from baseline, indicating a failure to respond appropriately to the changing value of the food reward^{18,47}.

associated with food reward; there is no requirement to assign any particular value to the food, to distinguish between different foods, or to update those representations. By contrast, current stimulus–value associations require the acquisition and rapid updating of a representation of reinforcer value, and the linking of this to object representations. Rapidly updated stimulus–value associations that support instrumental behaviour and

goal-directed action are mediated by the basolateral complex of the amygdala.

Central to the idea of current stimulus–value associations is their intimate connection with the representation of the reward (or, more generally, the goal) itself. Two types of behavioural assay — reinforcer devaluation and second-order conditioning — most readily show properties of current stimulus–value associations. In both of these experimental paradigms, behavioural performance seems to depend on the capacity of the stimulus to evoke a representation of the current value of the reinforcer. For instance, pairing the ingestion of a food reinforcer with malaise (induced by injections of lithium chloride) in rats will reduce subsequent responding to a stimulus (a CS) that has been paired with that food⁴⁴. That the reduction in the value of the food reward reduces conditioned responding to a CS indicates that, when the CS is presented, it evokes a representation of the food reward; because the value of this reward has been reduced, responding is decreased^{45,46}. This effect is abolished by neurotoxic lesions of the basolateral but not the central amygdala²⁶. Importantly, rats with basolateral amygdala lesions acquired the association between the CS and reward, as shown by their response to the food cup during CS presentation. This is the same type of food-generated response that we discussed earlier, and operates in the absence of the amygdala. In addition, the reduction in the value of the food reward that had been paired with lithium chloride was effective in the rats with lesions of the basolateral amygdala, as the rats avoided consuming the food pellets when they were presented in the home cage. So, the impairment in the rats with basolateral amygdala lesions seems to be specific to the ability of the CS to access a representation of the current value of the reward.

Similarly, monkeys with neurotoxic lesions of the amygdala seem to be insensitive to changes in the value of a reinforcer. In monkeys, studies have used ‘selective satiation’, rather than the pairing of food ingestion with the injection of lithium chloride, to devalue a reinforcer. In one task, monkeys are offered a series of choices between pairs of familiar objects, each of which has been associated with one of two different foods. For example, monkeys could be given a series of trials in which they are required to choose between ‘peanut objects’, which cover a half-peanut, and ‘fruit-snack objects’, which cover a fruit snack. Whichever item is chosen and displaced dictates the type of food reward that the monkey will obtain. Before some of these test sessions, monkeys are allowed to eat as much of one of the two types of food as they will consume (the selective satiation procedure; FIG. 2); in these sessions, intact monkeys tend to avoid choosing objects that cover the food on which they have been sated. Monkeys with neurotoxic lesions of the amygdala do not show this effect; they choose objects that are paired with each food reward just as they do in baseline test sessions that are not preceded by selective satiation¹⁸. In the absence of current stimulus–value associations, their behaviour is guided by stimulus–value associations that are acquired during discrimination learning, perhaps those that are intrinsic to the cortex.

A similar effect has been observed following **CROSSED DISCONNECTION** of the amygdala in one hemisphere and the orbital prefrontal cortex in the other hemisphere⁴⁷; in this study, the associations between the objects and reinforcers were acquired before the surgical disconnection was completed. Crossed disconnection allows the determination of whether two structures interact in a particular behaviour⁴⁸. It seems that, following the lesion, either the stored information about reward value cannot be updated, or else any successfully updated information about reward value cannot affect response selection. This effect does not seem to reflect an impairment in food choice or preference *per se*, because monkeys with bilaterally symmetrical amygdala lesions or orbital prefrontal cortex lesions express stable patterns of food preference among different food reinforcers^{14,47,49,50}. Furthermore, the effect cannot be ascribed to altered motivational states: again, monkeys with either bilateral lesions of the amygdala, or crossed disconnection of the amygdala and the orbital prefrontal cortex, will work as much as intact subjects to obtain food rewards^{27,47}.

Neurophysiological experiments provide further clues about the nature of reward representation in the amygdala, and what the unique properties of the amygdala in representing reward might be, compared with regions that are connected to the amygdala, such as the orbital frontal cortex. Recording of neuronal activity in the amygdala reveals that these neurons generally have complex properties. For example, the monkey amygdala contains neurons that respond exclusively to visual, auditory or somatosensory stimuli, cells that are multimodal, cells that respond specifically to particular biologically relevant sounds or objects (such as visual stimuli that are associated with food or juice), and cells that respond selectively to faces^{51–53}. The activity of neurons that fire selectively in response to food can be modulated by manipulating the affective significance of the food. For example, a neuron might fire strongly in response to the sight of watermelon and after the ingestion of the melon, but firing is sharply reduced after a piece of salted watermelon is presented⁵¹ (but see REF. 54). Notably, these neurons are found in the basomedial and basolateral nuclei⁵¹, consistent with a role for this region in mediating reinforcer-devaluation effects; that is, the effects of current versus consistent valuation. Similar effects of altering the affective significance of reward on neuronal firing are found in prefrontal cortex, both in response to the rewarding stimuli themselves and in the modulation of other neuronal firing properties in this region^{30,34,55}. For example, the activity of prefrontal cortex neurons during the delay period of a delayed-response task is stronger when the monkey expects a highly preferred reward at the end of the delay period than when it expects a less preferred reward³⁴. In addition, some neurons in the orbital prefrontal cortex are sensitive to reinforcer-specific satiety⁵⁶ and alter firing rates to a given reward if a new preferred reward becomes available³⁰. The interaction of amygdala and prefrontal cortex is considered in greater detail below.

CROSSED-DISCONNECTION LESION

This involves crossed unilateral lesions of two neural structures, one in each hemisphere of the brain. Because each hemisphere has one of the two structures intact, communication between the two structures is selectively disrupted. This procedure is commonly carried out to determine whether two brain structures functionally interact in a particular behaviour.

Another crucial aspect of current stimulus–value associations is the ability of the representation of reward that is evoked by a stimulus to support new learning — a capacity that is also dependent on the basolateral amygdala. In second-order conditioning, a neutral stimulus is paired directly with a reinforcer, and then this CS, now referred to as the first-order CS, is paired with a second neutral stimulus, the second-order CS. Intact animals show Pavlovian conditioned responding to the second-order CS, even though it has never been directly paired with primary reinforcement. For example, a light is paired with the delivery of food pellets. Rats will develop conditioned responding to the light (the first-order CS) and approach the food cup during light presentation. Subsequently, trials are introduced in which a new stimulus (for instance, a tone) is followed by the light, but the light is not followed by food when it is preceded by the tone. Even though the tone (the second-order CS) is never paired with food delivery, but only with the light, rats will start to approach the food cup during tone presentation. So, the light seems to have acquired some of the reinforcing power of the food reward it was paired with, in that it can support new conditioning on its own; it has become a secondary reinforcer. The first-order CS can also support the acquisition of an instrumental response. For example, rats will press a lever to gain presentation of the first-order CS (the conditioned-reinforcement procedure). Again, the lever press is never (or only rarely) paired with food or any other primary reinforcer. These phenomena indicate that the first-order CS has itself acquired reinforcing power as a consequence of its association with primary reinforcement. However, in both of these examples, first-order CSs do not acquire reinforcing power when the basolateral amygdala is removed or inactivated^{26,57} (FIG. 3). The interaction of the basolateral amygdala with the nucleus accumbens seems to be essential for this type of learning^{58–60}.

Another phenomenon that seems to be based on current stimulus–value associations is the potentiation of feeding by a CS in rats that are already sated. Hungry rats are trained that a CS (for example, a tone) signals food-pellet delivery. In a subsequent test session, rats that have eaten their fill of their normal diet in the home cage are presented with a dish of pellets (the reward associated with the CS) in either the presence or absence of the tone CS. Presentation of the tone CS stimulates feeding in intact rats, but not in rats with basolateral amygdala lesions⁶¹. In this case, as in the examples described above, it is assumed that the CS has failed to acquire reinforcing properties by virtue of its association with the food.

Whether the basolateral amygdala is required to maintain the representation of reward value that is associated with a CS once it has been acquired is less clear. To what extent are current stimulus–value associations essential for the stimulus to gain access to the representation of a reward and, by extension, its reinforcing power? Rats that are trained to associate a light with food reinforcement preoperatively, and then trained in a conditioned-reinforcement procedure after lesions of

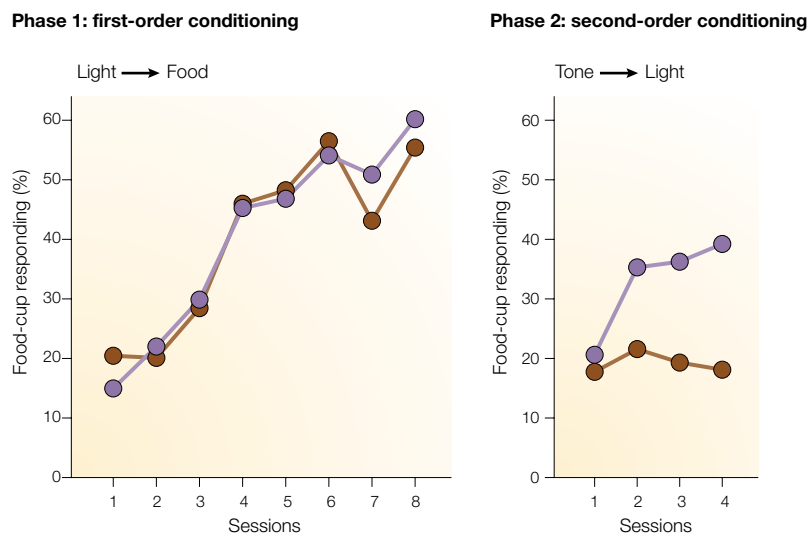


Figure 3 | **Second-order conditioning.** In phase 1 of the experiment, intact rats (purple circles) and rats with basolateral amygdala lesions (reddish-brown circles) receive first-order pairings of a conditioned stimulus (a light) with food. After experience with the light–food pairings, both groups of rats learn a conditioned response — in this case, approaching and entering the food cup during the light presentation, before the food is delivered. In phase 2, the same rats receive second-order light–tone pairings (a tone followed by a light) in the absence of food. Intact rats acquire second-order conditioned food-cup responses to the tone, but rats with lesions of the basolateral amygdala complex do not. The results indicate that, in rats with basolateral amygdala lesions, unlike intact rats, the light conditioned stimulus failed to acquire reinforcing value when it was paired with food. Data from REF. 26; figure reproduced, with permission, from REF. 89 © 1999 Elsevier Science.

the basolateral amygdala, are impaired in learning to press a lever to gain exposure to the light^{22,58,59,62}. Similar findings have been reported in marmoset monkeys with neurotoxic lesions of the amygdala⁶³. In this study, monkeys were trained to touch one side of a touch-sensitive screen for delivery of a conditioned reinforcer (a tone) that was paired with delivery of a small amount of banana milkshake. Preoperatively, the monkeys learned to press the screen up to five times, each time receiving the tone-conditioned reinforcer, before they received the milkshake reward. They reacquired this behaviour after receiving neurotoxic amygdala lesions; then the number of touches that were required to gain the tone was gradually increased, as was the number of presentations of the tone-conditioned reinforcer before milkshake was delivered. Monkeys with amygdala lesions were impaired in responding under this taxing schedule, indicating that the conditioned reinforcer was unable to support their behaviour to the same extent as in the control monkeys and, therefore, that it had lost its reinforcing power⁶³. These studies indicate that the absence of current stimulus–value associations weakens or eliminates the ability of stimuli that are paired with reward to support new associative learning themselves. That is, the remaining extra-amygdalar stimulus–value associations cannot support the process. However, monkeys with neurotoxic lesions of the amygdala efficiently learned new visual discriminations for auditory secondary reinforcers on which they had been trained before surgery¹⁸. Furthermore, rats with basolateral amygdala lesions developed normal second-order Pavlovian conditioned responses to a first-order CS that had been paired with

food before the lesion surgery⁶⁴. It seems that, at least in some instances, once a stimulus is associated with a representation of reward value, this representation can be maintained in the absence of the basolateral amygdala.

Parkinson *et al.*⁶³ articulate a distinction between the ‘predictive’ and ‘affective’ properties of a secondary reinforcer, which we think might correspond, respectively, to the properties of reinforcer value that are contained in cortical stimulus–value associations and the basolateral-amygdala-dependent current stimulus–value associations described above. They draw this distinction to explain the difference between their finding that secondary reinforcers seem to be insufficient to maintain responding to a visual stimulus in marmoset monkeys with amygdala lesions, and the finding that rhesus monkeys with neurotoxic lesions of the amygdala learn new visual-discrimination problems for auditory secondary reinforcement normally¹⁸. In other words, there seems to be a dissociation between the ability of a CS (a secondary reinforcer) to guide choice behaviour, because the presence of that secondary reinforcer is associated with the eventual delivery of primary reinforcement, and the reinforcing properties of the CS (secondary reinforcer) itself, which would be necessary to maintain responding during long schedules that must be completed before the delivery of primary reinforcement.

At present, it is not clear why predictive associations of a stimulus with reward — those that do not access current stimulus–value associations — are insufficient to support behaviour during the conditioned-reinforcement procedure, and the question of when an affective representation of reinforcer value is required (relative to a predictive one) remains open. An important prerequisite for progress in this area would be the development of a litmus test to ascertain whether a CS or a secondary reinforcer has affective reinforcing power, predictive reinforcing power, or both.

The central nucleus. Pavlovian approach (and avoidance) responses to specific CSs engage the central nucleus of the amygdala. In this type of stimulus–reward association, a stereotyped response to a previously neutral stimulus comes to be elicited by the pairing of reward with that stimulus^{5,65}. These behaviours are similar to simple conditioning, in that they reflect the acquisition of responses during CS presentation by virtue of the association between the CS and the reinforcer. However, as noted above, these behaviours are directed at the CS itself, rather than being associated with the reinforcer. For instance, in conditioned orienting, rats will increase their rearing response to a light as the light becomes associated with food delivery. This rearing response is a normal response of rats to a new visual stimulus, but it usually habituates rapidly. During a 10-s light presentation, rats commonly respond to the light with rearing behaviour for about the first 5 s, and spend the second 5 s approaching the food cup⁶⁶. Central nucleus lesions abolish conditioned orienting, although responding to the food cup is still intact²⁵. This type of stimulus–reward learning seems to operate through modulation of nigrostriatal dopamine projections by the central nucleus of the

amygdala⁶⁷. Similarly, in a classical-conditioning procedure that is intended to assess stimulus–reward associations, rats are presented with two visual stimuli (identical vertical white rectangles), one on either side of a food cup. Presentation of the stimulus on one side of the food cup (for example, on the left) is always followed by food delivery, whereas presentation of the stimulus on the other (right) side is never followed by food delivery. Although no response is required, rats learn to approach the stimulus when it appears on the left, but not the right; this behaviour, called ‘autoshaping’ or Pavlovian approach, reflects a Pavlovian association between the stimulus and food delivery⁶⁸. Autoshaping of approach to a light is also disrupted by central nucleus lesions⁶⁹, and involves the anterior cingulate cortex and the core (but not the shell) region of the nucleus accumbens⁷⁰. Notably, neither of these behaviours is impaired following lesions of the basolateral nucleus of the amygdala^{26,61,69}, reflecting the double dissociation between the basolateral and the central nuclei with regard to these two uses of stimulus–value associations.

Although we describe stimulus–value associations that are processed by the central nucleus as being distinct from those of the cortex — mainly on the basis of the kinds of behavioural response that they elicit — nothing in the foregoing discussion excludes the possibility that the central nucleus simply provides a motor output for stimulus–value associations that are stored elsewhere. Perhaps the central nucleus allows associations that are stored elsewhere to gain access to certain types of motor response, in contrast to our view that the central nucleus maintains or mediates distinct stimulus–value associations. Important evidence against this possibility comes from a recent study by Setlow and co-workers⁶⁰. Their rats with crossed unilateral lesions of the basolateral amygdala and the nucleus accumbens showed normal first-order conditioning, but impaired second-order conditioning, as assessed by food-cup responding. Remarkably, however, these rats developed normal conditioned orienting to the second-order CS, presumably mediated by the intact basolateral–central amygdala connections in the hemisphere with the nucleus accumbens lesion. This dissociation indicates that the central nucleus is involved in forming its own stimulus–value associations on the basis of current stimulus–value associations, which are provided by the basolateral amygdala.

Interestingly, some behaviours that are mediated by the central nucleus can be modulated by reinforcer-devaluation manipulations^{44,71}. Whether these effects are due to the central nucleus directly accessing the current value of the reinforcer, or reflect instead the influence of current stimulus–value associations that are processed by the basolateral amygdala, is unknown. That is, are the stimulus–value associations that are used by the central nucleus more like those processed by the basolateral amygdala, or like those held in cortical regions? A crucial experiment would be to examine the effect of devaluation on behaviours that are mediated by the central nucleus (such as conditioned orienting) in the absence of the basolateral complex.

Amygdala–prefrontal interactions

Patients with bilateral amygdala damage show poor judgement in making personal decisions in the social domain. They also perform poorly on formal tasks that require the integration of information about imagined wins and losses in the financial domain. These effects are similar to those associated with damage to the prefrontal cortex, particularly the VENTROMEDIAL PREFRONTAL CORTEX (including the orbital prefrontal cortex). For example, in a laboratory-based gambling task that was devised by Bechara *et al.*⁷², subjects are allowed to choose from any of four decks of cards, two of which provide a net gain and two of which provide a net loss in imagined monetary proceeds. Although control subjects learn to choose cards from the two decks that ultimately provide a net gain, patients with damage to either the amygdala or the ventromedial prefrontal cortex fail to do so. Consistent with these findings, several studies in both humans and non-human animals indicate that the amygdala is important for guiding response selection in conditions in which subjects must assess the relative risks and benefits of choices, or must deal with changing outcomes of choices. However, the precise nature of this contribution remains elusive.

Bechara *et al.*⁷³ have proposed that the essential contribution of the amygdala to the gambling task is in evoking the emotion (in their terminology, the ‘somatic state’) that is appropriate to winning or losing. According to this view, only if a subject can evoke the affective state that is appropriate to the occurrence of wins and losses can the emotion be used to guide responses in the face of future predicted wins and losses. Evidence for a failure of patients with bilateral amygdala damage to evoke the appropriate emotions can be found in their lack of changes in skin-conductance response (SCR) on receipt of wins or losses in the gambling task. Intact subjects show increased SCRs — a measure of arousal — after wins or losses, whereas patients with bilateral amygdala damage do not⁷⁴. Other measures that might be indicative of a particular affective state include heart and respiration rate, cutaneous blood flow, blood pressure and other autonomic responses. Although damage to the ventromedial prefrontal cortex (including the orbital frontal cortex) also impairs performance on the gambling task, these subjects do generate appropriate SCRs after wins or losses⁷³. This dissociation indicates that information about the affective state of winning or losing is generated in the amygdala, rather than in the prefrontal cortex.

The reinforcer-devaluation tasks that we discussed earlier incorporate an element of the gambling task: a representation of the value of the outcome is required for subjects to perform accurately or appropriately, although, in this case, the outcome is deterministic not probabilistic. In the study by Baxter *et al.*⁴⁷, monkeys with crossed disconnection of the amygdala in one hemisphere and the orbital prefrontal cortex in the other hemisphere were impaired in their ability to respond appropriately in the face of changing values of reward outcomes. Whereas intact monkeys tended to avoid choosing objects that covered a devalued food,

VENTROMEDIAL PREFRONTAL CORTEX

The regions of the cerebral cortex on the ventral and medial surfaces of the frontal lobes, including the orbital frontal cortex, the gyrus rectus and the anterior cingulate cortex. ‘Orbital frontal’ or ‘orbital prefrontal’ cortex usually refers more specifically to the cortex on the orbital surface of the frontal lobe, including Walker’s areas 10, 11, 13 and 14.

monkeys with either bilateral amygdala lesions¹⁸ or with the crossed amygdala–orbital prefrontal disconnection⁴⁷ tended to choose just as they had during the baseline conditions, in which foods were roughly equally preferred and valued. This result mirrors aspects of the Bechara *et al.* findings in humans performing the gambling task⁷², in the sense that neither monkeys nor humans seemed to take into account the value of the outcome of an action.

When viewed through the lens of guiding goal-directed behaviour, it is instructive to consider what effects of amygdala lesions can be ruled out. Can monkeys with amygdala removals distinguish between the values of different foodstuffs? Are they as motivated as intact monkeys to earn food rewards? The answer to both of these questions seems to be ‘yes’. As already indicated, monkeys with amygdala lesions, like intact monkeys, have distinct food-preference profiles^{14,27,50}. In addition, monkeys with amygdala lesions²⁷, and monkeys with the crossed disconnection of amygdala and orbital frontal cortex⁴⁷, will work as hard as intact monkeys to earn food rewards. So, global alterations in discriminating between foods or in motivational levels cannot account for the results of Málková *et al.*¹⁸ or of Baxter and colleagues⁴⁷. Furthermore, monkeys with amygdala lesions can learn even difficult tasks for food reward, so difficulty cannot account for the impairments. As already mentioned, these findings support the idea that the amygdala is important in representing the value of particular reinforcers, and for associating these representations with stimuli. However, when considered together with studies of human neuropsychology, these findings take on a new significance: the representations that require the amygdala are an essential part of the brain system that guides choice behaviour and response selection. This conclusion is a long way from the characterization of the amygdala as important for processing information about fear, or about emotional learning more generally.

Neurophysiological recordings in rats reveal firing patterns in the amygdala that are consistent with a role of the amygdala, along with prefrontal cortex, in hypothesis testing and response selection. Specifically, Schoenbaum *et al.*^{75–77} tested rats on a go–no-go olfactory-discrimination task, in which they sampled an odour stimulus on each trial. Subsequently, they were able to poke at a fluid port for a fluid reinforcer. Responses to the correct odour were rewarded with a palatable 10% sucrose solution; responses to the incorrect odour (errors of commission) were punished with a distasteful quinine solution. During learning, the rats would initially respond to both the correct and incorrect odours on all trials, and would gradually begin to withhold responding to the incorrect odour. The experimental design allowed the authors to analyse neural activity after a fluid-port response had been made, but before the reinforcer was delivered, and to examine neural activity during odour sampling and reinforcer delivery.

Populations of neurons in the amygdala and orbital frontal cortex encoded the expected outcome of the fluid-port response⁷⁵. So, neurons fired differentially during the period after the fluid-port response, but

before fluid delivery, depending on whether the fluid that would be delivered was sucrose or quinine (FIG. 4). Remarkably, this differential firing emerged before animals were able to reliably discriminate between the correct and incorrect odours behaviourally (that is, correctly withhold fluid-port responses on trials in which the incorrect odour was presented). Firing of neurons in the basolateral amygdala and orbital frontal cortex also differentiated between the correct and incorrect odour during the odour-sampling phase; neurons fired differentially depending on whether an odour was associated with sucrose or quinine, in many cases independently of the particular identity of the odour. Neurons in the basolateral amygdala were particularly prone to reverse their firing correlates when the odour–reinforcer associations were reversed during training⁷⁵.

Most importantly, these two neuronal populations were largely independent of each other. That is, only about one-quarter of the neurons in the basolateral amygdala and orbital frontal cortex that fired in anticipation of sucrose or quinine after a fluid-port response, also fired during sampling of the incorrect odours. Hence, the neural representation of the outcome associated with a particular stimulus, and of the outcome itself, are largely independent of one another. This finding is consistent with the idea that a stimulus can be associated with reinforcement independently of the representation of the reinforcement itself, such that these two representations can potentially be accessed and manipulated independently.

Stimulus–value associations and their use

As we have seen, the amygdala is just as important for the processing of positive affect and reward as it is for the processing of negative affect. Stimulus–value associations are of obvious benefit. Pavlovian associations, for example, are built on associating neutral stimuli with stimuli that activate autonomic pathways and trigger innate action patterns that are associated with ingestive behaviour. Consistent with this view, the central nucleus of the amygdala, and anatomically related portions of the nucleus accumbens, influence behaviour in appetitive contexts by providing a link between environmental stimuli and those structures involved in the direct control of feeding behaviour, including approach to, and procurement of, nutrients and water. Stimulus–value associations that affect instrumental behaviour, on the other hand, guide choices between two or more stimuli (and perhaps also places, actions or other abstract goals). In this type of association, the amount of current biological value that is inherent in a stimulus is used to predict the outcome of an action produced in the context of that stimulus. Although the nature of the reward representation is unknown, recent work indicates that the basolateral amygdala is crucial for processing the sensory properties of food rewards²³. In this framework, the specific role of the basolateral amygdala in these appetitive contexts is to link initially neutral environmental stimuli with current biological value, thereby guiding response selection. Finally, the neocortex might help to represent stimulus value independently of the

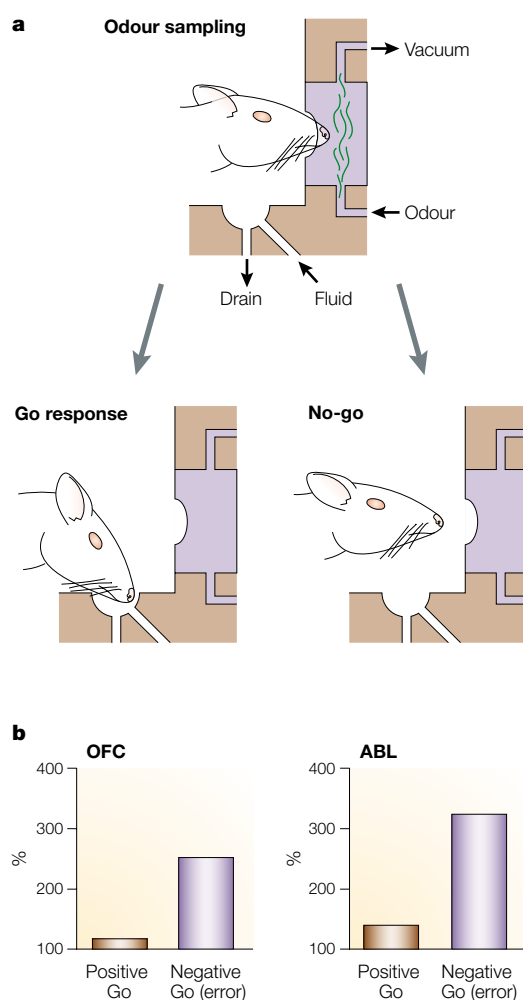


Figure 4 | Neuronal firing in the basolateral amygdala and the orbital frontal cortex during the delay portion of trials in a two-odour discrimination task. a | Task. In this task, a response to the fluid port after sampling of one odour led to delivery of a rewarding sucrose solution, whereas a response after sampling a second odour led to delivery of an aversive quinine solution. In solving each new odour discrimination, rats initially respond by entering the fluid port (a 'go' response) after odour sampling on every trial. Gradually, the rats learn to withhold this response (a 'no-go' response) after sampling the odour that predicted the aversive outcome. Reproduced, with permission, from REF. 76 © 1999 Society for Neuroscience. **b | Unit recording.** The activity of neurons recorded during the delay portion of trials in the two-odour discrimination task; that is, after the odour is sampled, but before the sucrose or quinine fluid is delivered. Bars show activity on 'go' trials only, and only on those trials performed before the rat had learned the task to a performance criterion. Activity is shown as a percentage of the pre-trial baseline firing rates. In each case, neural activity was significantly higher than baseline for the negative 'go' trials (errors), and higher on negative 'go' trials relative to positive 'go' trials. In some tasks, rats were trained on a four-odour problem, and unit activity reflected the forthcoming fluid outcome rather than the particular odour used on that trial. So, neurons in the orbital frontal cortex (OFC) and the basolateral amygdala (ABL) discriminated between the positive (sucrose) and negative (quinine) outcomes of a trial before the rat was able reliably to withhold responding on the negative trials. Reproduced, with permission, from REF. 75 © 1998 Macmillan Magazines Ltd.

amygdala. Note that the existence of multiple mechanisms allows the historical value to be represented simultaneously with current (recent) value. In the devaluation paradigms that we have discussed, the animals must override amygdala-independent mechanisms that promote a given action on the basis of a history of reinforcement over the long term, in favour of the reinforcer. Identifying the conditions in which stimulus–reward associations work together, or not, and understanding how they guide behaviour in the real world, remains a goal for future research.

Some commonly used paradigms, such as conditioned place preference, are not easily categorized in the framework provided here. In conditioned place (or cue) preference, rats are given paired presentations; for example, food with place 1, no food with place 2. Later, they are given a choice between place 1 and place 2 (with no food present at either place), and the amount of time spent in each location is recorded. Intact rats spend more time in the place that had been paired with food ingestion than in the other place. Performance on this task is dependent on the basolateral amygdala^{78,79}; furthermore, it is subject to modulation by reinforcer devaluation⁸⁰. There is no *a priori* reason to expect that the basolateral amygdala would be essential for this task. Perhaps because there are relatively few pairings between reward and place, performance relies on current stimulus–value associations. Alternatively, during the test phase, the rats make a 'choice' (about where to be) in the sense used here, and this behaviour might evoke a representation of the goal (reward associated with a particular location), thereby engaging a current stimulus–value association.

The different forms of stimulus–value association that have been attributed to subregions of the amygdala probably do not provide us with a comprehensive account of the functions of these two subnuclei. For example, the central nucleus has a well-described role in modulating attentional processing, by outputs through basal forebrain cholinergic neurons to cortical regions^{81–84}. Furthermore, the involvement of the central nucleus in Pavlovian conditioning might extend to other situations in which the CS influences motor behaviour; for instance, Pavlovian instrumental transfer is impaired by central nucleus lesions⁸⁵. In this task, a rat learns to press a lever for food delivery. Subsequently, a CS (for instance, a tone) is paired with food delivery in the absence of the lever. Finally, the lever is returned to the test box and the rat is allowed to press it for food delivery. The rate of pressing is increased during CS presentation, indicating an influence of the Pavlovian tone–food association on instrumental (lever press–food) behaviour. This might reflect a general role of the central nucleus in mediating influences of conditioned stimuli (both appetitive and aversive) on motor behaviour⁵. Notably, if the task is designed in such a way as to require the current representation of a reinforcer, the phenomenon engages the basolateral amygdala as well²³, consistent with our hypothesis.

Future directions

Our discussion has emphasized aspects of reward processing in the amygdala and in connected structures, such as the orbital prefrontal cortex. It is clear from neuropsychological studies in humans and other animals, and from the results of behavioural neurophysiology, that the amygdala is crucial for certain aspects of reward representation and stimulus–reward learning.

We do not mean to belittle the role of the amygdala in other cognitive processes; for instance, in the production of fear responses, the emotional modulation of memory, social behaviour or attentional processing. Indeed, we believe that an important goal of future research will be to develop a unitary, integrative theory of amygdala function that can account for the diverse effects of amygdala damage on behaviour, taking into account the different functional roles of particular nuclei and their connections⁸⁶. Another goal of future research will be to explore the relationship between the

processing of positive and negative reinforcers by the amygdala. In some situations, the aspects of stimulus–reward learning that are ascribed to the different nuclei seem to operate for aversive stimuli as well as for appetitive ones⁶². By contrast, there is evidence that aversive and appetitive processing might be handled by different information-processing streams⁸⁷.

Both of these goals involve the search for conceptual affiliations between functions that are apparently disparate: affective and non-affective functions, positive and negative affect. Regardless of the outcome of this programme of research, neurobiological theory needs to accommodate the finding that the amygdala has an important role in both positive and negative affect, and in specific aspects of the processing of information about rewards, but not in reward processing in general. Moreover, it should entertain the idea that the specific function of the basolateral amygdala, at least, involves the updating of current representations of stimulus value.

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